AN UPDATE ON ACANTHOSIS NIGRICANS WITH SPECIAL REFERENCE TO HAIR-AN SYNDROME

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Acanthosis Nigricans (AN) is characterized by symmetrical, hyperpigmented, velvety plaques, hyperinsulinemia (1) and malignancy in some cases. The first documented case of AN was in 1889. In next ten years another fifty patients had been described. An association with internal malignancy was proposed. In 1976, Kahn et al published their landmark study in which the association between AN and insulin resistance was first described. Patients with AN have more chances of developing coronary artery diseases (2). As obesity is increasing in India and here in Kashmir it is expected that we would see more cases of AN (3). Thus the significance AN may be less for the dermatologists and much more for the physicians, endocrinologists and cardiologists.

Pathophysiology
AN is caused by factors that stimulate epidermal keratinocyte and dermal fibroblast proliferation. In the benign form of AN, the factor is probably insulin or an insulin-like growth factor that incites the epidermal cell propagation. In malignant AN, the stimulating factor is hypothesized to be a substance secreted either by the tumor or in response to the tumor. Exogenous medications also have been implicated as etiologic factors.

Frequency
The exact incidence of AN is unknown. It is seen in children too in 7.1% of normal population. But the incidence increases with obesity—more than one half of the adults who weigh greater than 200% of their ideal body weight have lesions consistent with AN. Type 2 diabetes is increasing in incidence in the United States, especially among black and Hispanic children; 60 to 92 percent of these children have acanthosis nigricans (4). The malignant form of AN is far less common, and, in one study, only 2 of 12,000 patients with cancer had signs of AN. The incidence of AN is equal for men and women. Malignant AN occurs more frequently in elderly persons; however, cases have been reported in children with Wilms tumor.

Mortality/Morbidity
AN is divided into 2 broad categories, benign and malignant. Patients with the benign form of AN experience very few complications of their skin lesions. However insulin resistance is common and ranges from an incidental finding on routine blood studies to overt diabetes mellitus and partial resolution may occur with treatment of the insulin-resistant state. Malignant AN is associated with significant complications because the underlying malignancy is often an aggressive tumor. Average survival time of patients with signs of malignant AN is 2 years, although cases in which patients have survived for up to 12 years have been reported.

Presentation
Patients in most cases are not aware and it is the physician who picks up the sing. This asymptomatic area of darkening and thickening of the skin may be associated with pruritus in some cases. Lesions begin as hyperpigmented macules and patches and progress to palpable plaques. The skin changes may precede, be associated or appear after any signs of cancer in one third of cases each. AN is characterized by symmetrical, hyperpigmented, velvety plaques that may occur in almost any location but most commonly appear on the intertriginous areas of the axilla, groin, and posterior neck (5). The posterior neck is the most commonly affected site in children. The vulva is the most commonly affected site in females who are hyperandrogenic and obese. Acrochordons (skin tags) are often found in and around the affected areas. Occasionally, lesions of AN may be present on the mucous membranes of the oral cavity, nasal and laryngeal mucosa, and esophagus. The areola of the nipple also may be affected. Eye involvement, including papillomatous lesions on the eyelids and conjunctiva, may occur. Nail changes, such as leukonychia and hyperkeratosis, have been reported. The lesions of malignant AN are clinically indistinguishable from the benign forms; however, one must be more suspicious if the lesions arise rapidly, are more extensive, are symptomatic, or are in atypical locations. Regression of AN has been seen with treatment of the underlying malignancy, and reappearance may suggest recurrence or metastasis of the primary tumor.

Types of AN
Eight types of AN have been described.

Obesity-associated AN, once labeled pseudo-AN, is the most common type of AN. Lesions may appear at any age but are more common in adulthood. The dermatosis is weight dependent, and lesions may completely regress with weight reduction. Insulin resistance is often present in these patients.

 Syndromic AN is the name given to AN that is associated with a syndrome. In addition to the widely recognized association of AN with insulin resistance, AN has been associated with numerous syndromes. The type A syndrome and type B syndrome are special examples. The type A syndrome also is termed the hyperandrogenemia, insulin resistance, and AN syndrome (HAIR-AN syndrome). This syndrome is often familial, affecting primarily young women (especially black women). It is associated with polycystic ovaries or signs of virilization (e.g., hirsutism, clitoral hypertrophy). High plasma testosterone levels are common. The lesions of AN may arise during infancy and progress rapidly during puberty. See below for details. The type B syndrome generally occurs in women who have uncontrolled diabetes mellitus, ovarian hyperandrogenism, or an autoimmune disease such as systemic lupus erythematosus, scleroderma, Sjogren’s syndrome, or Hashimoto thyroiditis. Circulating antibodies to the insulin receptor may be present. In these patients, the lesions of AN are of varying severity.

Acral AN (acral acanthotic anomaly) occurs in patients who are in otherwise good health. Acral AN is most common in dark-skinned individuals, especially those of African American descent. The hyperkeratotic velvety lesions are most prominent over the dorsal aspects of the hands and feet.

Unilateral AN, sometimes referred to as nevoid AN, is believed to be inherited as an autosomal dominant trait. Lesions are unilateral in distribution and may


become evident during infancy, childhood, or adulthood. Lesions tend to enlarge gradually before stabilizing or regressing.

**Familial AN** is a rare geno-dermatosis that seems to be transmitted in an autosomal dominant fashion with variable phenotypic penetrance. The presentation is similar to Unilateral AN.

**Drug-induced AN**, although uncommon, may be induced by several medications, including nicotinic acid, insulin, pituitary extract, systemic corticosteroids, and diethylstilbestrol. Rarely, triazinate, oral contraceptives, fusidic acid, and methyl testosterone also have been associated with AN. The lesions of AN may regress following the discontinuation of the offending medication.

**Malignant AN**, which is associated with internal malignancy, is the most worrisome of the variants of AN because the underlying neoplasm is often an aggressive cancer. Most common underlying cancer is tumor of the gut (90%) especially stomach cancer (69%), usually adenocarcinoma. In 25-50% of cases, lesions are present in the mouth. The tongue and the lips most commonly are affected with elongation of the filiform papillae on the dorsal and lateral surfaces of the tongue and multiple papillary lesions appearing on the commissures of the lips. Oral lesions of AN seldom are pigmented (6).

**Mixed-type AN** refers to those situations in which a patient with one of the above types of AN develops new lesions of a different etiology. An example of this would be an overweight patient with obesity-associated AN who subsequently develops malignant AN.

**Diagnosis**

For patients with adult onset of AN, perform a basic workup for underlying malignancy. Screen for diabetes with a glycosylated hemoglobin level or glucose tolerance test. Screen for insulin resistance; a good screening test for insulin resistance is a plasma insulin level, which will be high in those with insulin resistance. Histologic examination reveals hyperkeratosis, papillomatosis, and slight irregular acanthosis with minimal or no hyperpigmentation. The dermal papillae project upward as fingerlike projections, with occasional thinning of the adjacent epidermis. Pseudohorn cysts may be present. Clinical dyschromia is secondary to the hyperkeratosis and not to increased melanocytes or increased melanin deposition. Microscopically, acanthosis nigricans is characterized by an increased number of melanocytes, with papillary hypertrophy and hyperkeratosis. Associated hypertrophy and hyperkeratosis cause acanthosis nigricans to be palpable rather than macular (7).

**Treatment**

The goal of therapy is to correct the underlying disease process. Treatment of the lesions of AN is for cosmetic reasons only. Correction of hyperinsulinemia often reduces the burden of hyperkeratotic lesions. Likewise, weight reduction in obesity-associated AN may result in resolution of the dermatosis. No treatment of choice exists for AN.

**HAIR-AN Syndrome**

The hyperandrogenism, insulin resistance and acanthosis nigricans (HAIR-AN) syndrome is an unusual condition that affects females. Persons with the disorder usually present with obesity and insulin resistance during the prepubertal period. HAIR-AN syndrome is an acronym for an unusual multisystem disorder. The precipitating abnormality is thought to be insulin resistance, with a secondary increase in insulin levels and subsequent overproduction of androgens in the ovaries. Long periods of hyperinsulinism and hyperandrogenism can result in the cutaneous manifestation of acanthosis nigricans. Patients are often concerned about the physical manifestations of this disorder and may be less aware of systemic problems. Physicians should assess women with these problems for an underlying endocrine abnormality. Although a treatment regimen for the HAIR-AN syndrome has not been established, antiandrogen therapy and weight loss are useful.

**Clinical Manifestations (8)**

**Hyperandrogenism:**

- Hirsutism of the face, chin, chest, perineum
- Alopecia (hair loss from the vertex/crown areas of the scalp; bitemporal hair loss less frequent)

**Insulin resistance:**

- Polydipsia, polyuria (symptoms of insulin resistance are often subclinical)
- Acanthosis nigricans: Verrucous, velvety hyperpigmentation on nape of neck, vulva, axillae, groin, umbilicus, submammary regions; increased skin tags
- Obesity: Increased waist-to-hip ratio (android appearance)

To evaluate the possibility of hyperandrogenism, total testosterone (possibility of virilizing tumor) should be measured on two to three occasions. Levels of 17_**-hydroxyprogesterone (possibility of congenital adrenal hyperplasia), dehydroepiandrosterone sulfate (DHEAS) (possibility of androgen-producing tumor of the adrenal gland) and morning cortisol after a low dose of
dexamethasone should be determined (possibility of Cushing's syndrome), as should levels of luteinizing and follicle-stimulating hormones, depending on physical findings, history and concern about an ovarian or adrenal abnormality. Production of testosterone increases because 17-hydroxyprogesterone is an androgen precursor (9-11).

About 1 to 3 percent of women with hyperandrogenism are thought to have this condition, with many cases remaining undiagnosed. Occasionally, patients with autoimmune disorders such as Hashimoto's thyroiditis and Graves' disease also have HAIR-AN syndrome. Other nonmalignant endocrine disorders with features of androgen excess include Cushing's syndrome, polycystic ovary syndrome, acromegaly and congenital adrenal hyperplasia (12).

By being aware of HAIR-AN syndrome and its associated conditions, the clinician can diagnose and treat the more serious underlying endocrine disorder. Weight loss is proved to improve insulin resistance. Diet restriction is therefore important. Metformin has been used with success.

References:

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Conflict of Interest: None

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